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(54) Title: TREATMENT OF DIABETIC NEUROPATHY

(57) Abstract

Topical use of insulin in the treatment of diabetic neuropathy in a patient.

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"TREATMENT OF DIABETIC NEUROPATHY"

FIELD OF THE INVENTION.

This invention relates to the treatment of diabetic neuropathy, and in particular it relates to a novel method and composition for the topical treatment of this condition.

BACKGROUND OF THE INVENTION.

Diabetic neuropathy (also known as diabetic neuritis) is a painful condition suffered by many diabetic patients, and arises from nerve dysfunction particularly at the extremities of the body such as the toes and feet.

Table 1 outlines the Classification and Staging of Diabetic Neuropathy, based on the recommendations[1] of the American Diabetes Association, 1988. The first of two main pathological disturbances of normal nerve function in diabetes involves a postulated relationship between raised blood glucose levels (hyperglycaemia), the polyol pathway (the biochemical pathway triggered by high glucose levels and producing alcohol-sugars called polyols as the end-products), myo-inositol (a cell energy-storage substrate), Na^+/K^+ ATPase (ion-pump enzyme) activity and nerve conduction, that is, the speed of nerve impulse transmission (Greene *et al.*[2]).

The second postulated patho-physiological mechanism of disturbance of normal nerve function in diabetes relates to lack of oxygen within the nerve fibres, which is chemically-induced by raised blood sugar levels and activation of the polyol pathway, leading to changes in blood flow through micro-vessels within the nerves (Williamson *et al.*[3]).

TABLE 1 Classification and staging of diabetic neuropathy[1] (based on recommendations of the American Diabetes Association, 1988).

Class 1 : Subclinical Neuropathy

A. Abnormal electrodiagnostic tests:

1. Decreased nerve conduction velocity.
2. Decreased amplitude of evoked muscle or nerve action potential.

B. Abnormal quantitative sensory testing:

1. Vibratory/tactile.
2. Thermal warming/cooling.

C. Abnormal autonomic function tests:

1. Diminished sinus arrhythmia (beat to beat heart rate variation).
2. Diminished sudomotor function.
3. Increased pupillary latency.

Class 2 : Clinical Neuropathy

A. Diffuse neuropathy:

1. Distal symmetric sensorimotor polyneuropathy.
2. Autonomic neuropathy
   - a. abnormal pupillary function,
   - b. sudomotor dysfunction,
   - c. genitourinary autonomic neuropathy,
     - i bladder dysfunction
     - ii sexual dysfunction
   - d. gastrointestinal autonomic neuropathy
     - i gastric atony
     - ii gall bladder atony
     - iii diabetic diarrhoea
   - e. cardiovascular autonomic neuropathy
   - f. hypoglycaemic unawareness.

B. Focal neuropathy:

1. Mononeuropathy/mononeuropathy multiplex.
2. Plexopathy.
3. Radiculopathy.
4. Cranial Neuropathy.

Methods of directly (via the lining cells of the blood vessels) and indirectly (via the finest skin sensory nerves) stimulating the skin flushing response using electrical current (iontophoresis) and measurement of changes in skin blood flux (by laser Doppler velocimetry) are known and these techniques have been employed by others[4,5,6], and by the inventor and colleagues[7,8].

The treatments used in the prior art for the management of diabetic neuropathy have been recently reviewed by Pfeifer *et al.*[9,10] (1993), who describe three different clinical patterns and detail algorithms for their diagnosis and management.

Listed below are the types of treatments most commonly used in management of painful diabetic neuritis or neuropathy (some of which are mentioned by Pfeifer[9,10]):

(a) **Physical therapies** applied to the affected painful region may sometimes provide symptomatic relief, e.g.

i electrical stimulation such as TENS, interferential, vibration, ultrasound

ii massage and rubbing

iii hydrotherapy

iv application of warmth, heat or cold

v acupuncture or acupressure

vi application of Opsite dressing film[11,12].

(b) **Drugs and medications to be taken by mouth for pain relief:**

i *non-steroidal analgesics* (e.g. aspirin, paracetamol, ibuprofen, ketoprofen, etc.);

ii *narcotics*, e.g codeine, morphine, pethidine, and sustained release morphine preparations;

iii *antidepressants* including tricyclics such as amitryptilline, etc.;

iv *anticonvulsants* with inhibitory effects on relay of pain signals, such as carbamazepine, clonazepam;

v *antiarrhythmic compounds* which reduce electrical excitability of cells such as mexilitene, lignocaine;

vi *aldose reductase inhibitors*, such as Sorbinil, ponalrestat (ICI), epalrestat (Ono), tolrestat (Wyeth-Ayerst), zopolrestat (Pfizer) which may improve the levels of intraneural energy substrate (myinositol), reduce polyol sugar accumulation (sorbitol), and improve Na^+/K^+ ATPase function;

vii *supplementary medication* providing essential fatty acids (which are reduced in diabetes, e.g. gamma-linolenic acid (GLA) as Evening Primrose oil[13,14].

(c) **Compounds (by injection) to promote neural regeneration**, (i.e. repair, regrowth and reconnection);

- such as gangliosides (Cronassial), vitamin B12 (cyanocobalamin), and insulin-like growth factors.

(d) **Topical treatments to desensitise superficial nerve fibres** conveying pain signals, e.g.

i *capsaicin* cream or ointment (usually as 0.025% or 0.075%) which is a neurotoxin and has been used for post-herpetic neuralgia[15,16,17], and for painful diabetic neuropathy[18].

ii *aspirin* in vanishing cream or sorbolene has been reported by Kassirer[19] to relieve post-herpetic neuralgia, and has been used by the present inventors (Westerman and Zimmet, unpublished) and found to be sometimes effective in the burning painful diabetic neuropathy.

It has now been discovered that topical application of insulin can be used as a specific treatment of painful diabetic neuropathy. Topical insulin therapy has not been reported previously, particularly in treatment of diabetic neuropathy.

In 1980, Snyder & Kim[20] made the first suggestion that insulin may be a nerve survival factor. Soon after, Low *et al.*[4] described the reduced responses to sudomotor axon reflex tests as a small fibre dysfunction in neuropathy, and electrically evoked axon reflex responses were found to be reduced in diabetes mellitus[7], and largely restored by a single dose of insulin in rat experimental STZ-diabetes[21]. In seeking a possible *modus operandi* for insulin, Waldbillig and LeRoith's demonstration of insulin receptors on peripheral nerves[22], and Llewellyn *et al.*'s localisation of these[23], led to investigations by the present inventor for a role of insulin in normal sensory nerve function[24].

The technique of transdermal iontophoresis in dermatology[25] has been shown to be effective in facilitating transport of peptides[26], including insulin[27,28]. The present inventor has conducted studies of the short-term effects of insulin on small nerve and axon reflex function in both animal studies in streptozotocin-induced diabetic rats and insulin-dependent diabetic patients[29]. In both diabetic humans and rats, the size of the skin flushing response to noxious stimulation (termed "axon reflex flare") was significantly reduced, although responses of small blood vessels themselves were not reduced. This indicates that the reduced inflammation was due to sensory nerve dysfunction rather than microvascular impairment. Topical application of insulin by six minutes of cathodal electrical current, termed iontophoresis, resulted in highly significant restoration of the size of the axon reflex, both in humans with IDDM and in rats made diabetic chemically with streptozotocin. The immediate restorative effect of the insulin iontophoresis indicates that the decline in the axon reflex is reversible, and therefore due to functional changes in the nerves mediating the response, rather than any structural defects. Mechanisms by which insulin produces these acute effects on nerves are now known, but the rapid time-course of the effect (in minutes) suggests some ionic or excitability changes, such as calcium levels within the nerves based on other indirect evidence of such actions of insulin[30,31].

It is generally accepted that to date no specific treatment of painful diabetic neuropathy exists. All the treatments currently in use (discussed above) are aimed at providing symptomatic relief. Some of these are also aimed at identifiable physiological disturbances which occur in diabetes to variable extent and for which no specific tests or assessments exist.

SUMMARY OF THE INVENTION.

In its broadest aspect, the present invention provides the topical use of insulin in the treatment of diabetic neuropathy in a patient.

In one aspect, the present invention provides a method for the treatment of diabetic neuropathy in a patient which comprises the topical administration of a therapeutically effective amount of insulin to the affected area of skin of the patient.

In another aspect, the present invention provides a composition for the treatment of diabetic neuropathy in a patient, which comprises a therapeutically effective amount of insulin in a topical, pharmaceutically acceptable diluent or carrier.

In yet another aspect, the present invention provides the use of a therapeutically effective amount of insulin in the manufacture of a medicament for topical use in the treatment of diabetic neuropathy in a patient.

DETAILED DESCRIPTION OF THE INVENTION.

Preferably, the insulin used in accordance with this invention is human insulin (available, for example, as Humulin R, Velosulin or Actrapid). It is to be understood, however, that the present invention also extends to the use of porcine insulin, bovine insulin or insulin from other non-human animal species.

The term "insulin" as used herein is intended to encompass not only insulin *per se*, but also the α- or β-subchains of insulin, separately or in combination.

In accordance with this invention, the insulin is administered in therapeutically effective amounts. A therapeutically effective amount means that amount necessary at least partly to attain the desired effect, or to delay the onset of, inhibit the progression of, or halt altogether, the onset or progression of the diabetic neuropathy condition being treated. Such amounts will depend, of course, on the particular condition being treated, the severity of the condition and individual patient parameters including age, physical condition, size, weight and other concurrent treatment. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is preferred generally that a minimum effective dose be used according to sound medical judgement. It will be understood by those of ordinary skill in the art, however, that a higher dose may be administered for medical reasons, psychological reasons or for virtually any other reasons.

The formulation of preparations or compositions for topical administration is well known to persons skilled in this field. Suitable pharmaceutically acceptable carriers and/or diluents include any and all conventional solvents, dispersion media, fillers, aqueous solutions, antibacterial and antifungal agents, absorption promoting agents, and the like. The use of such media and agents for pharmaceutically active substances is well known in the art, and it is described, by way of example, in *Remington's Pharmaceutical Sciences*, 18th Edition, Mack Publishing Company, Pennsylvania, USA. Except insofar as any conventional media or agent is incompatible with the active ingredient, use thereof in the pharmaceutical compositions of the present invention is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

The topical preparations contemplated by the present invention include aqueous cream, ointment, gel, lotion, roll-on liquid, spray, glass bead wound

dressing, synthetic polymer dressing impregnated with insulin, or any other method of transdermal application of insulin. The cream will include buffering agents and hydrophobic ingredients. These preparations may also include the use of compounds such as DMSO (dimethylsulfoxime) which would facilitate the passage of insulin across the skin keratin barrier and into epidermis.

Since a cream is likely to prove most efficacious in promoting transfer of the insulin active ingredient across and into the affected skin, a detailed description of the method of preparing a cream is included herein by way of example.

Topical Insulin Cream. 70g of vanishing cream base (such as Home Brand skin repair cream, Sorbolene cream, or Cetomacrogol cream) containing purified water, stearic acid, dimethicone, isopropyl myristate, cetyl alcohol, triethanolamine, polysorbate 80, aloe vera extract, methyl paraben, propyl paraben, fragrance. Add 70 IU or 210 IU of Humulin R, Velosulin or Actrapid - all of which are neutral human monocomponent insulin, 100 IU per ml, in sodium phosphate buffer, preservatised by meta-cresol 0.3%. This gives a final concentration of 1 or 3 IU per gram of finished cream.

From preliminary tests the final formula of the vanishing cream base appears relatively unimportant as to the efficacy of the cream. A different type of Sorbolene lotion has also been used as the vehicle and is effective. It contains de-ionised water, glycerine, sorbitol, light mineral oil, cetyl alcohol, cetomacrogol 1000, stearic acid, triethanolamine, tocopheryl acetate, imidazolidinyl urea, methyl paraben, EDTA, para-cresol. A similar but more hydrophobic and pH-buffered cream is now being developed.

Suitably, the topical preparation of this invention is applied at least daily, or several times daily, to the affected area of the skin of the patient. By way of example, the application may be applied twice daily (morning and night), or even three times daily.

Effective treatment begins with careful selection of suitable patients having diabetic neuropathy and symptoms associated with small fibre dysfunction. The clinical picture for which the topical insulin treatment is most appropriate and most likely to benefit is that particular neuropathy symptom-complex involving superficial burning type of discomfort with dysesthesia or paraesthesia (Pfeifer *et al.*[9,10]). Patients with non-insulin dependent diabetes and not previously insulin-treated are most suitable.

The topical insulin cream is applied at twice daily frequency restricted to skin areas with superficial burning discomfort. This is most commonly the toes, feet and lower parts of legs.

Re-measurement of thermal perception thresholds on treated skin zones at monthly intervals is performed according to the methods described by Jamal *et al.*[32,33,34] and Delaney *et al.*[6,24] using the Medelec TTT device. Both cold and warm perception thresholds are measured.

The clinically observable effect apart from pain relief (symptom score), is a reduction in thermal perception threshold, which may be interpreted as an improved thermal sensory acuity. This may be related to an improved sensory nerve function. Cold threshold improves more rapidly than warm threshold, suggesting greater benefit for the myelinated A-delta nerve fibres mediating cold sensation.

Preferred aspects of the topical use of insulin in the treatment of diabetic neuropathy include the following:

i The insulin concentration in a cream may range from 0.01-20 IU per gram, preferably 0.1-10 IU per gram, more preferably 1-3 IU per gram.

ii The amount of cream applied is usually about 0.5g on each foot/leg. The consistency of the preferred cream tends to be a little sloppy, and it is therefore easily spread and rubbed into the skin until it has vanished.

iii The recommended application frequency is twice to thrice daily, but after longer-term trials, a lesser frequency such as once daily might be acceptable for maintenance therapy or skin ulcer prophylaxis.

iv Symptomatic patients, particularly those with type 2 (non-insulin-dependent) diabetes mellitus most suitable for treatment with topical insulin cream are identified after a careful history of symptoms (see Pfeifer algorithm[9,10]) and testing for neuropathy with a group of investigations. These include testing small sensory nerve function by pinprick and cotton-wool sensibility, and warm and cold perception thresholds at wrist and foot dorsum, and AC-current perception thresholds (250 Hz or 5Hz). Larger nerve fibres are tested by sensory and motor nerve conduction/emg studies of lower limb (sural, peroneal TA, EDB), and by measuring vibration sensitivity with biothesiometer, as well as AC-current perception thresholds at higher frequencies such as 2000 Hz.

v Body weight, height, body mass index (BMI), abdominial circumference, fasting plasma glucose and insulin and haemoglobin A_1C are also measured to provide an indication of insulin sensitivity in type 2 subjects and quality of glycemic control in both type 1 and 2 subjects. Euglycemic clamp measurements have not yet been used in these studies for logistic reasons.

vi Warm and cold thresholds are usually elevated if small fibre dysfunction is provoking a burning discomfort of affected skin.

vii Current perception thresholds determined at lower frequency stimulation (such as 250 Hz, 5Hz) should provide another quantitative measure of small sensory nerve fibre function[35,36,37,38].

Suitable topical vehicles for use in administration of insulin accordance with this invention, and methods of preparation thereof, include the following:

1. Vanishing creams:

(i) Cetomacrogol cream

Peptide	qs
Cetomacrogol emulsifying wax	15
Liquid paraffin (by weight)	10
Chlorocresol	0.1
Propylene glycol	5
Distilled water to	100

Melt the cetomacrogol emulsifying wax with paraffin at about 70°C. Dissolve the chlorocresol and propylene glycol in about 50 parts of the distilled water warmed to about the same temperature. Mix, adjust to weight and stir until cool. Then add the peptide in appropriate concentration, and mix thoroughly.

(ii Aqueous Cream APF

Peptide	qs
Emulsifying ointment	30
Glycerol	5
Phenoxyethanol	1
Distilled water to	100

Melt the emulsifying ointment at about 70°C. Dissolve the phenoxyethanol in the distilled water, warmed to about the same temperature. Mix, adjust to weight and stir until cool. Add the peptide, stirring thoroughly.

(iii) Buffered Cream BPC 73

Peptide	qs
Citric acid	5
Sodium phosphate	25
Chlorocresol	1
Emulsifying ointment	300
Distilled water	669

Melt the emulsifying ointment with the aid of gentle heat, add the sodium phosphate, the citric acid and the chlorocresol, previously dissolved in the

distilled water at the same temperature, and stir gently until cold. Add the peptide and mix very well.

2. Ointments

(i) Emulsifying Ointment APF

Peptide	qs
Emulsifying wax	30
White soft paraffin	50
Liquid paraffin (by weight)	20

Melt together and stir until cool. Add the peptide in appropriate concentration in a portion of the base and then gradually incorporate the remainder, mixing thoroughly.

(ii) Peptide Ointment - as in Neomycin and Bacitracin Ointment BPC 73

Peptide	qs
Liquid paraffin	10
White soft paraffin to	100

Melt the white soft paraffin, incorporating the liquid paraffin, and stir until cold. Titurate the drug with a portion of the base and gradually incorporate the remainder of the base.

3. Gels.

(i) Peptide Gel - as used in Lignocaine and Chlorhexidine Gel APF

Peptide	qs
Tragacanth	2.5
Glycerol	25
Distilled water to	100

Mix the tragacanth with the glycerol and add most of the distilled water. Heat to boiling, cool, add peptide, adjust to weight and mix well. Protect finished product from light.

4. Sprays.

(i) - as used in Adrenaline and Atropine Spray BPC 73

Peptide	qs
Sodium metabisulphite	1
Chlorbutol	5
Prophylene glycol	50
Distilled water to	1000

(ii) - as used in Indospray

Peptide	qs

Alcohol	95%

5. Lotions

(i) - as used in Aminobenzoic Acid Lotion BPC 73

Peptide	qs
Glycerol	20
Alcohol 95%	60
Distilled water to	100

(ii) - Cetomacrogol Lotion APF

Peptide	qs
Cetomacrogol emulsifying wax	3
Liquid paraffin	10
Glycerol	10
Chlorhexidine gluconate solution	0.1
Distilled water to	100

Melt the cetomacrogol emulsifying wax with the liquid paraffin at about 60°C and add, with rapid stirring, to the chlorhexidine solution previously diluted to 50 parts with distilled water at the same temperature. Mix, adjust to volume and stir until cold.

Throughout this specification unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

In the accompanying drawings,

Figures 1 to 3 show graphically the results of topical insulin treatment of painful burning feet in cases of diabetic neuropathy selected according to the criteria previously described (see page 10, paras. iv, v and Pfeifer[9,10]).

Further features of the present invention are more fully described in the following Example(s). It is to be understood, however, that this detailed description is included solely for the purposes of exemplifying the present

invention, and should not be understood in any way as a restriction on the broad description of the invention as set out above.

EXAMPLE

A preliminary open trial of topical insulin treatment for painful peripheral neuropathy has been conducted.

All subjects were selected using Pfeifer's criteria[9,10] and had painful sensory polyneuropathy complicating their diabetes. This was confirmed by a battery of neurophysiological tests including sensory and motor NCVs with action potential latencies and amplitudes, vibration perception threshold using a Biothesiometer, warm and cold thermal thresholds at the wrist and on the foot dorsum using the Medelec TTT device and, in many of the patients, current perception thresholds on index finger and great toe using the Neurometer CPT at 2000 Hz, 250 Hz, 5Hz.

Topical insulin cream of the composition described above (1 IU insulin per gram of finished cream) was provided to the patients, with instructions to apply about 0.5g on each foot/leg two or three times daily.

The results are shown in the Figures. Figures 1 and 2 relate to a maximum number of 30 Type 2 diabetic subjects who had not been treated with systemic insulin. Figure 3 depicts the results from a maximum of 16 subjects who had received systemic insulin treatment.

On all graphs, the vertical axis depicts the thermal threshold: open rectangles being the warm perception threshold, black filled rectangles being the cold threshold. The severity of the painful burning symptoms on a 10 point visual analogue scale is also shown on the vertical axis by the filled black circles. The horizontal axis shows the duration of treatment at which the tests

and re-tests were performed. The horizontal dotted line shows the upper limit of the normal 95% confidence margin (mean + 2.2 standard deviations).

Figure 1 shows the results from 12 weeks treatment, the number of subjects being 30 for weeks 0 and 4 and decreasing progressively to 16 at week 12. It will be noted that with topical insulin treatment, statistical significance for both symptom score improvement and improved function in the delta sensory fibres has been achieved by 4 weeks and improves progressively beyond that.

Figure 2 graph shows on a time scale of months the same trends, and it will be noted that warm threshold has become significantly improved (i.e. WPT reduced) by 4 months of treatment.

Thus, from the data of Figures 1 and 2 it is clear that in these non-insulin dependent diabetic patients with burning painful neuropathic symptoms there is symptomatic relief and thermal acuity confirmation of improved sensory nerve function in both classes of small sensory nerve fibres. The most dramatic result is in the cold fibres and is accompanied by most of the patients reporting an awareness of improved general sensation in their feet, a deterioration of numbness and an improvement in the ability to feel socks, carpet and other surfaces upon which they are walking. This could involve some improvement in large sensory fibre function, but has not yet been measured.

Figure 3 shows the results of treatment of a smaller group of patients who had received systemic insulin treatment. These include some patients with Type 2 DM, whose deterioration ultimately required systemic insulin treatment; the remainder include patients with Type 1 DM. The lack of improvement in thermal threshold results for warm and cold in this group contrasts markedly with those from the previous group, but also surprising is the symptomatic improvement noted by these patients.

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CLAIMS:

1. A method for the treatment of diabetic neuropathy in a patient, which comprises the topical administration of a therapeutically effective amount of insulin to the affected area of skin of the patient.

2. A method according to claim 1 wherein the insulin is human insulin.

3. A method according to claim 1 wherein the insulin is porcine insulin, bovine insulin or insulin from other non-human animal species.

4. A method according to any of claims 1 to 3, wherein the insulin comprises the α- and/or β-subchains.

5. A method according to any of claims 1 to 4, wherein the insulin is topically applied as a cream, ointment, gel, spray or lotion.

6. A method according to claim 5, wherein the insulin is topically applied in a vanishing cream base.

7. A method according to any of claims 1 to 6, wherein the insulin is applied as a cream comprising from 0.01-20 IU per gram, preferably 0.1-10 IU per gram, most preferably 1-3 IU per gram.

8. A method according to claim 7, wherein the cream is applied in an amount of approximately 0.5 gram at a frequency of 2-3 times daily.

9. Use of a therapeutically effective amount of insulin in the manufacture of a medicament for topical use in the treatment of diabetic neuropathy in a patient.

10. A composition for the treatment of diabetic neuropathy in a patient, which comprises a therapeutically effective amount of insulin in a topical, pharmaceutically acceptable diluent or carrier.

11. A composition according to claim 10, wherein the insulin is human insulin.

12. A composition according to claim 10, wherein the insulin is porcine insulin, bovine insulin or insulin from other non-human animal species.

13. A composition according to any of claims 10 to 12, wherein the insulin comprises the α- and/or β-subchains.

14. A composition according to any of claims 10 to 13, wherein the insulin is formulated as a cream, ointment, gel, spray or lotion.

15. A composition according to claim 14, wherein the insulin is formulated in a vanishing cream base.

16. A composition according to any of claims 10 to 15, wherein the insulin comprises from 0.01-20 IU per gram, preferably 0.1-10 IU per gram, most preferably 1-3 IU per gram.

FIG 1

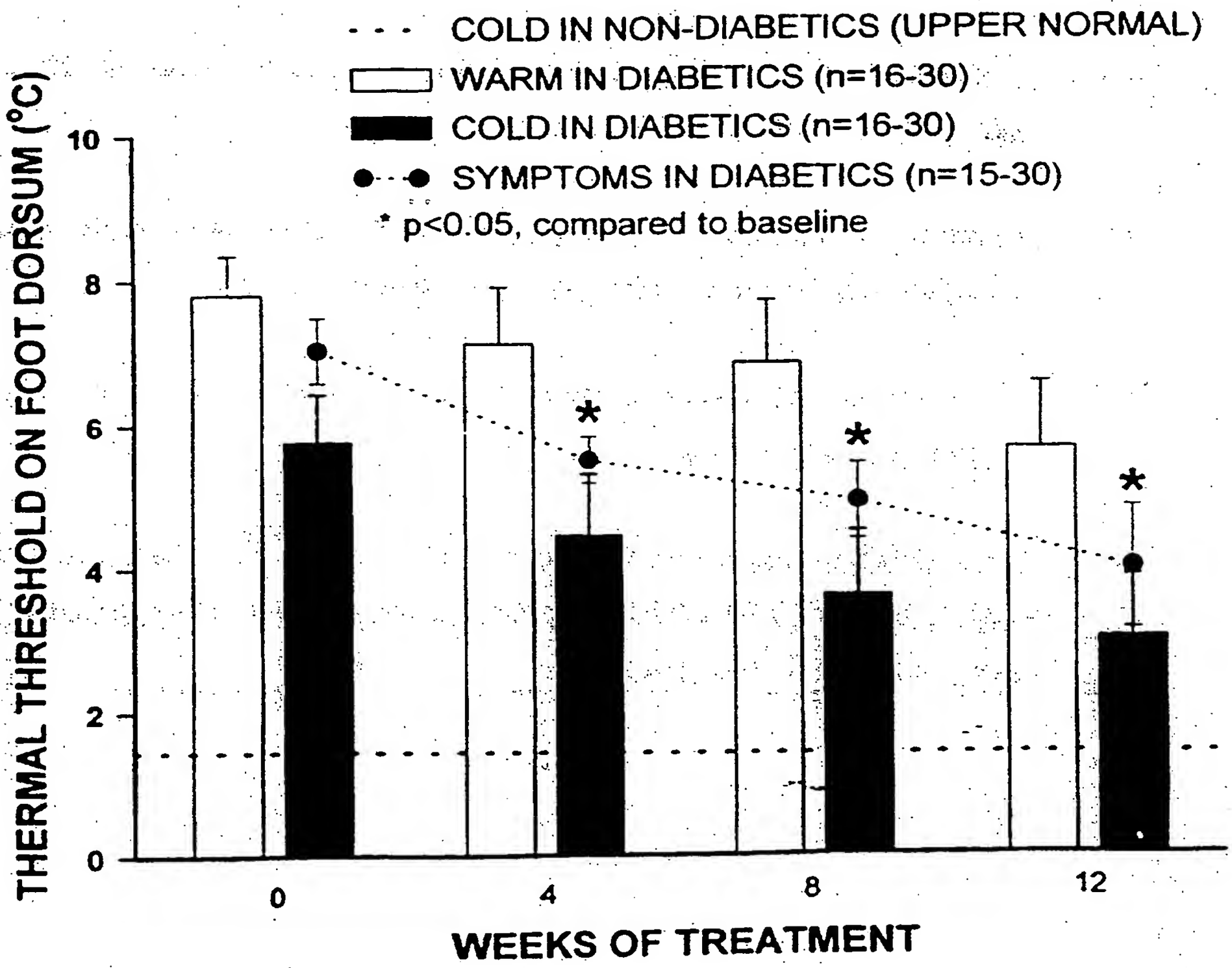


FIG 2

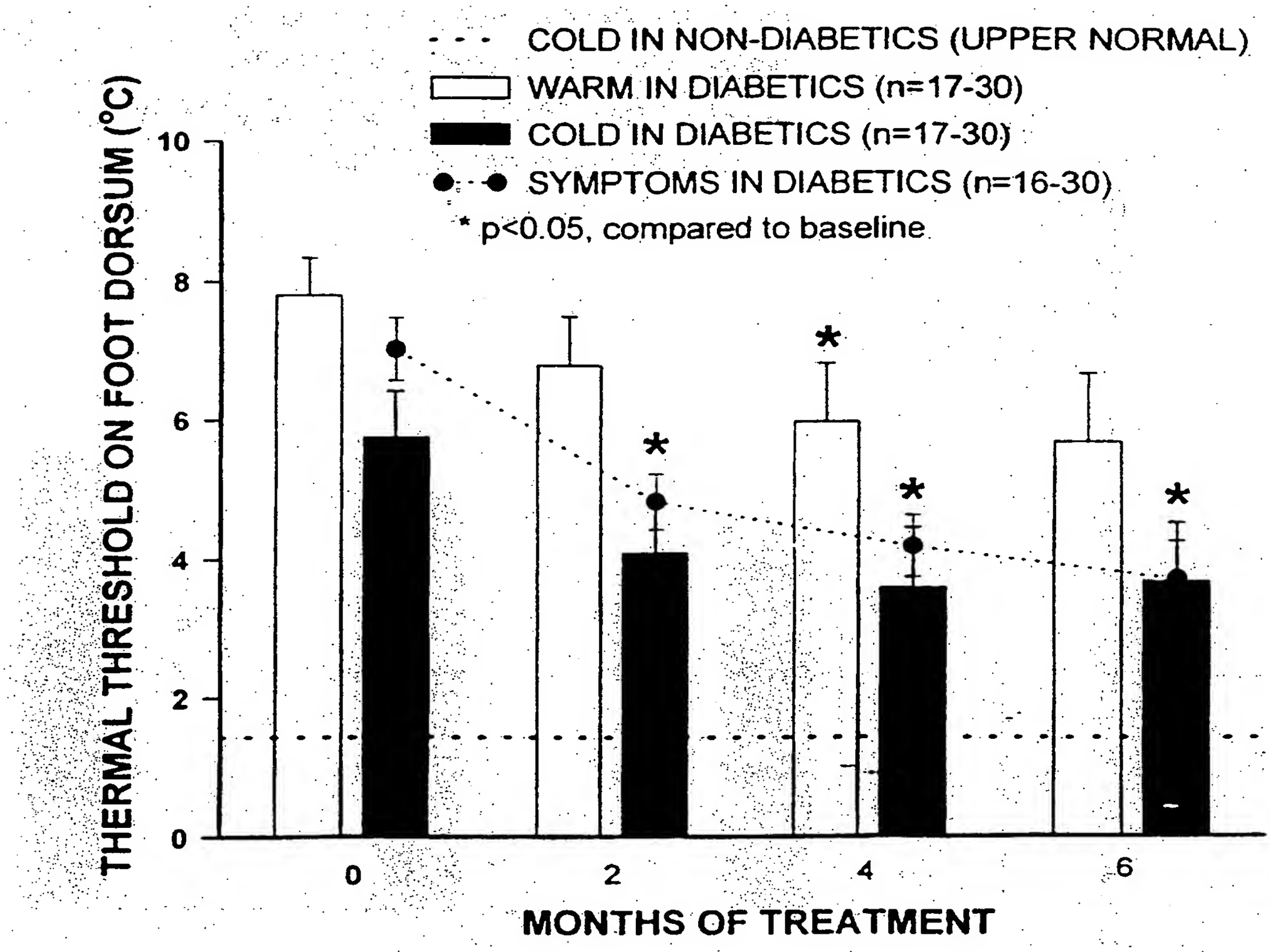
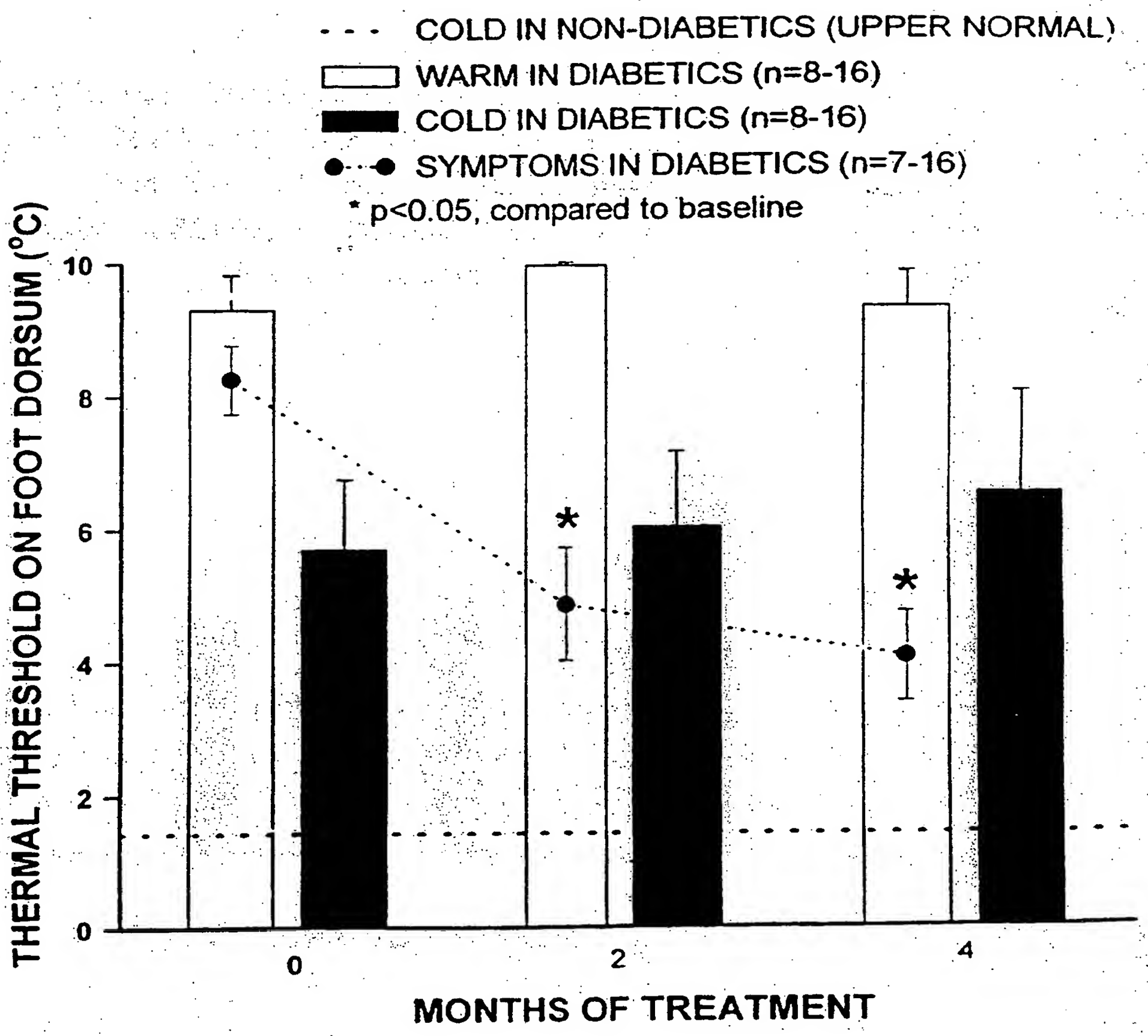

COLD IN NON-DIABETICS (UPPER NORMAL)
WARM IN DIABETICS (n=17-30)
COLD IN DIABETICS (n=17-30)
SYMPTOMS IN DIABETICS (n=16-30)
* p<0.05, compared to baseline
THERMAL THRESHOLD ON FOOT DORSUM (°C)
10
8
6
4
2
0
0
2
4
6
MONTHS OF TREATMENT

FIG 3


COLD IN NON-DIABETICS (UPPER NORMAL)
WARM IN DIABETICS (n=8-16)
COLD IN DIABETICS (n=8-16)
SYMPTOMS IN DIABETICS (n=7-16)
* p<0.05, compared to baseline
THERMAL THRESHOLD ON FOOT DORSUM (°C)
10
8
6
4
2
0
0
2
4
MONTHS OF TREATMENT

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 96/00046

A. CLASSIFICATION OF SUBJECT MATTER

Int Cl[6]: A61K 38/28, 9/06, 9/107, 9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC[6] A61K 38/28, IPC[5] A61K 37/26; Chemical Abstracts

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
DERWENT; WPAT; JPAT; Chemical Abstracts; CASM; Medline A61K, insulin, diabet:, neuro:, nerve#, brain, topic: gel, cream, ointment, spray, lotion

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	AU,A,41366/85 (Geriaco AG) published 24 October 1985, see the examples in particular	1-16
X,Y	JP,A,04-149126 (Mitsubishi Kasei Corp.) published 22 May 1992 and Patent Abstracts of Japan, vol. 112C, 983. See Abstract.	1-16
X,Y	DD,A1,254881 (Technische Universität Dresden) published 16 March 1988. See Abstract.	1-16

[X] Further documents are listed in the continuation of Box C

[X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
28 March 1996

Date of mailing of the international search report
11TH. APRIL 1996.

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/AU 96/00046

C (Continuation) **DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	EP,A1,561330 (Liedtke, Rainer K., Dr.) published 22 September 1993. See column 4, second paragraph in particular.	1-16
X,Y	AU,A,42925/85 (The Trustees of Columbia University of the City of New York) published 21 November 1985. See the examples in particular.	1-16
X,Y	US,A,5145679 (Hinson) published 8 September 1992, See example 2 in particular.	1-16
P,X,Y	FR,A,2710529 (Zirinis, Phedon and Slama, Gerard) published 7 April 1995. See example 4.	1-16
P,X,Y	FR,A,2710530 (Zirinis, Phedon and Slama, Gerard) published 7 April 1995. See example 4.	1-16
Y	Dunlop, M.E. et al. (1988) The Influence of insulin and sorbinil on myoinositol uptake in peripheral nerve from normal and diabetic rats and a neuroblastoma cell line (NIE-115), *Diabetes Research*, volume 8 no. 2, pages 51-57. See entire article.	1-16
X,Y	Ryszka, F. and Tatomir-Szmyt, I. (1992) Influence of selected tensides on insulin release from ointment, *Ann. Acad. Med. Siles.*, volume 25, pages 37-40. See the summary.	1-16
X,Y	Ryszka, F. et al. (1993) The release of ^{125}I-labelled insulin from ointment invitro and in vivo, *Boll. Chim. Farmaceutico*, volume 132 no. 6, pages 197-200. See whole document.	1-16
X,Y	Chandrashekar, G. et al. (1994) Optimization of parameters for transdermal permeation of insulin, *Indian J. Pharm. Sci.*, volume 56(6), pages 205-209. See whole document.	1-16
X,Y	Ryszka, F. and Galoch, B. (1990) Pharmaceutical availability of insulin from ointment, *Ann. Acad. Med. Siles.*, volume 20, pages 39-43. See summary.	1-16
X,Y	Machida, Y. (1993) Development of topical drug delivery systems utilizing polymeric materials, *Yakugaku Zasshi*, volume 113 no. 5, pages 356-368. See summary.	1-16
X,Y	Kazim, M. et al. (1984) Effect of topical insulin on blood glucose of diabetic mice, *Surgical Forum*, pages 64-67. See whole document.	1-16
X,Y	Ryden, L. and Edman, P. (1992) Effect of polymers and microspheres on the nasal absorption of insulin in rats, *International Journal of Pharmaceutics*, volume 83, pages 1-10. See summary.	1-16

ISDOCID: <WO___9623522A1_I_>

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ AU 96/00046

C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	Pillion, D.J. et al. (1991) Systemic absorption of insulin delivered topically to the rat eye, *Investigative Ophthalmology and Visual Science*, volume 32 no. 12, pages 3021-3027. See abstract.	1-16
X,Y	Pillion, D.J. et al. (1994) Alkylglycosides enhance systemic absorption of insulin applied topically to the rat eye, *The Journal of Pharmacology and Experimental Therapeutics*, volume 271 no. 3, pages 1274-1280. See abstract.	1-16
X,Y	Hayakawa, E. et al. (1992) Conjunctival penetration of insulin and peptide drugs in albino rabbit, *Pharmaceutical Research*, volume 9 no. 6, pages 769-775. See abstract.	1-16
X,Y	Yamamoto, A. et al. (1989) The ocular route for systemic insulin delivery in the albino rabbit, *The Journal of Pharmacology and Experimental Therapeutics*, volume 249 no. 1, pages 249-255. See abstract.	1-16
X,Y	Nomura, M. et al. (1994) Effect of addition of hyaluronic acid to highly concentrated insulin on absorption from the conjunctiva in conscious diabetic dogs, *J. Pharm. Pharmacol.*, volume 46, pages 768-770. See abstract.	1-16
X,Y	Bartlett, J.D. et al. (1994) Toxicity of insulin administered chronically to human eye in vivo, *Journal of Ocular Pharmacology*, volume 10 no. 1, pages 101-107. See abstract.	1-16
Y	Sotelo, J.R. et al. (1991) An in vitro model to study diabetic neuropathy, *Neurosci. Lett.*, volume 129 no. 1, page 91-94. See whole document.	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.
PCT/AU 96/00046

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
AU	41366/85	AU	41366/93	CA	1243948	DK	1730/84
		EP	162007	JP	60233018		
JP	04-149126						
DD	254881						
EP	561330	DE	4208552	JP	6316530		
AU	42925/85	EP	178321	WO	8505036		
US	5145679	WO	9310795				
FR	2710529	FR	2710530				
FR	2710530	FR	2710529				

END OF ANNEX